(FILE 'HOME' ENTERED AT 09:01:45 ON 06 SEP 2002)

INDEX '1MOBILITY, AGRICOLA, AQUASCI, BIOTECHNO, COMPENDEX, COMPUAB, CONF, CONFSCI, ELCOM, EVENTLINE, HEALSAFE, IMSDRUGCONF, ISMEC, LIFESCI, OCEAN, MEDICONF, PASCAL, PAPERCHEM2, POLLUAB, SOLIDSTATE, ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, ...' ENTERED AT 09:02:25 ON 06 SEP 2002

SEA GRAFT OR TRANSPLANTATION OR TRANSPLANT

81	FILE 1MOBILITY
5101	FILE AGRICOLA
2178	FILE AQUASCI
33247	FILE BIOTECHNO
9440	FILE COMPENDEX
74	FILE COMPUAB
78	FILE CONF
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326	FILE EVENTLINE
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2917	FILE PAPERCHEM2
234	FILE POLLUAB
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56617	FILE USPATFULL
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            3384   FILE BIOTECHDS
           16631   FILE CABA
            1235   FILE CEABA-VTB
            2374   FILE CIN
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             548   FILE DRUGUPDATES
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              94   FILE VETB
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           43756   FILE WPIDS
           43756   FILE WPINDEX
L1              QUE GRAFT OR TRANSPLANTATION OR TRANSPLANT
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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, DGENE, CAPLUS, PASCAL,
     CANCERLIT, TOXCENTER, ESBIOBASE, JICST-EPLUS, USPATFULL, WPIDS,
     BIOTECHNO, PROMT, LIFESCI, ADISALERTS, DRUGU, NLDB, CABA, IFIPAT,
     COMPENDEX, CONFSCI, DRUGB, BIOBUSINESS, PHIN, FEDRIP, ...' ENTERED AT
     09:03:49 ON 06 SEP 2002
                E HORWITZ DAVID?/AU
L2          30181 S L1 (S) (PERIPHERAL BLOOD MONONUCLEAR CELLS OR PBMC OR CD4 OR
L3           7545 S L2 (S) (CYTOKINE OR MITOGEN OR IL-2 OR TGF, OR TGF? OR IL-10
L4             59 S L3 (S)((GRAFT VERSUS HOST) OR GVH OR GVHD) (S) (TGF OR TGF?
L5             20 DUP REM L4 (39 DUPLICATES REMOVED)

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WEST Search History

DATE: Friday, September 06, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
L7	L6 same TGF	1	L7
L6	L4 same ((graft versus host) or GVH or GVHD)	29	L6
L5	L4 same (graft versus host) or GVH or GVHD	1023	L5
L4	L3 same (cytokine or mitogen or IL-2 or TGF, or TGF? or IL-10, or IL-15 or (CON adj A) or (anti adj cd3) or (anti adj cd28) or (anti adj cd2) or SEB or (staphlococcus enterotoxin B))	108	L4
L3	L2 same (peripheral blood mononuclear cells or PBMC or CD4+ or cd8+ or cD3+Cd4-cd8- or double negative or DN or dns)	385	L3
L2	(graft or transplantation or transplant)	117697	L2
L1	Horwitz-David-$.in.	8	L1

END OF SEARCH HISTORY

ibib abs 1-20

L5 ANSWER 1 OF 20 MEDLINE
ACCESSION NUMBER: 2002364721 IN-PROCESS
DOCUMENT NUMBER: 22102034 PubMed ID: 12106494
TITLE: The potential of human regulatory T cells generated ex vivo as a treatment for lupus and other chronic inflammatory diseases.
AUTHOR: Horwitz David A; Gray J Dixon; Zheng Song
CORPORATE SOURCE: The Division of Rheumatology and Immunology, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.. dhorwitz@hsc.usc.edu
SOURCE: ARTHRITIS RESEARCH, (2002) 4 (4) 241-6.
Journal code: 100913255. ISSN: 1465-9905.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Editorial
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20020712

AB Regulatory T cells prevent autoimmunity by suppressing the reactivity of potentially aggressive self-reactive T cells. Contact-dependent **CD4**+ CD25+ 'professional' suppressor cells and other **cytokine**-producing **CD4**+ and **CD8**+ T-cell subsets mediate this protective function. Evidence will be reviewed that T cells primed with transforming growth factor (**TGF**)-**beta** expand rapidly following restimulation. Certain **CD4**+ T cells become contact-dependent suppressor cells and other **CD4**+ and **CD8**+ cells become **cytokine**-producing regulatory cells. This effect is dependent upon a sufficient amount of **IL**-**2** in the microenvironment to overcome the suppressive effects of **TGF**-**beta**. The adoptive transfer of these suppressor cells generated ex vivo can protect mice from developing chronic **graft**-**versus**-**host** disease with a lupus-like syndrome and alter the course of established disease. These data suggest that autologous T cells primed and expanded with **TGF**-**beta** have the potential to be used as a therapy for patients with systemic lupus erythematosus and other chronic inflammatory diseases. This novel adoptive immunotherapy also has the potential to prevent the rejection of allogeneic **transplants**.

L5 ANSWER 2 OF 20 MEDLINE
ACCESSION NUMBER: 2002434242 IN-PROCESS
DOCUMENT NUMBER: 22178609 PubMed ID: 12191961
TITLE: The pathogenesis of oral lichen planus.
AUTHOR: Sugerman P B; Savage N W; Walsh L J; Zhao Z Z; Zhou X J; Khan A; Seymour G J; Bigby M
CORPORATE SOURCE: AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451, USA.
SOURCE: CRITICAL REVIEWS IN ORAL BIOLOGY AND MEDICINE, (2002) 13 (4) 350-65.
Journal code: 9009999. ISSN: 1045-4411.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Dental Journals; Priority Journals
ENTRY DATE: Entered STN: 20020823
Last Updated on STN: 20020823

AB Both antigen-specific and non-specific mechanisms may be involved in the pathogenesis of oral lichen planus (OLP). Antigen-specific mechanisms in OLP include antigen presentation by basal keratinocytes and antigen-specific keratinocyte killing by **CD8**(+) cytotoxic T-cells. Non-specific mechanisms include mast cell degranulation and

matrix metalloproteinase (MMP) activation in OLP lesions. These mechanisms may combine to cause T-cell accumulation in the superficial lamina propria, basement membrane disruption, intra-epithelial T-cell migration, and keratinocyte apoptosis in OLP. OLP chronicity may be due, in part, to deficient antigen-specific **TGF**-beta1-mediated immunosuppression. The normal oral mucosa may be an immune privileged site (similar to the eye, testis, and placenta), and breakdown of immune privilege could result in OLP and possibly other autoimmune oral mucosal diseases. Recent findings in mucocutaneous **graft-versus-host** disease, a clinical and histological correlate of lichen planus, suggest the involvement of TNF-alpha, CD40, Fas, MMPs, and mast cell degranulation in disease pathogenesis. Potential roles for oral Langerhans cells and the regional lymphatics in OLP lesion formation and chronicity are discussed. Carcinogenesis in OLP may be regulated by the integrated signal from various tumor inhibitors (**TGF**-beta1, TNF-alpha, IFN-gamma, IL-12) and promoters (MIF, MMP-9). We present our recent data implicating antigen-specific and non-specific mechanisms in the pathogenesis of OLP and propose a unifying hypothesis suggesting that both may be involved in lesion development. The initial event in OLP lesion formation and the factors that determine OLP susceptibility are unknown.

L5 ANSWER 3 OF 20 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002236745 EMBASE
TITLE: The potential of human regulatory T cells generated ex vivo as a treatment for lupus and other chronic inflammatory diseases.
AUTHOR: Horwitz D.A.; Gray J.D.; Zheng S.G.
CORPORATE SOURCE: Dr. D.A. Horwitz, The Division Rheumatology/Immunology, Department of Medicine, University of Southern California, Los Angeles, CA, United States. dhorwitz@hsc.usc.edu
SOURCE: Arthritis Research, (2002) 4/4 (241-246).
Refs: 60
ISSN: 1465-9905 CODEN: ARRECG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Regulatory T cells prevent autoimmunity by suppressing the reactivity of potentially aggressive self-reactive T cells. Contact-dependent **CD4**(+) CD25(+) professional suppressor cells and other **cytokine**-producing **CD4**(+) and **CD8**(+) T-cell subsets mediate this protective function. Evidence will be reviewed that T cells primed with transforming growth factor (**TGF**)-.**beta**. expand rapidly following restimulation. Certain **CD4**(+) T cells become contact-dependent suppressor cells and other **CD4**(+) and **CD8**(+) cells become **cytokine**-producing regulatory cells. This effect is dependent upon a sufficient amount of **IL-2** in the microenvironment to overcome the suppressive effects of **TGF**-.**beta**.. The adoptive transfer of these suppressor cells generated ex vivo can protect mice from developing chronic **graft versus host** disease with a lupus-like syndrome and alter the course of established disease. These data suggest that autologous T cells primed and expanded with **TGF**-.**beta**. have the potential to be used as a therapy for patients with systemic lupus erythematosus and other chronic inflammatory diseases. This novel adoptive immunotherapy also has the potential to prevent the rejection of allogeneic **transplants**.

L5 ANSWER 4 OF 20 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002105812 MEDLINE
DOCUMENT NUMBER: 21823159 PubMed ID: 11835352
TITLE: Granulocyte-colony stimulating factor enhances the

expression of transforming growth factor-beta mRNA in CD4-positive peripheral blood lymphocytes in the donors for allogeneic peripheral blood stem cell transplantation.

AUTHOR: Hirayama Yasuo; Sakamaki Sumio; Matsunaga Takuya; Kuroda Hiroyuki; Kusakabe Toshiro; Akiyama Takehide; Kato Junji; Kogawa Katsuhisa; Koyama Ryuzo; Nagai Tadanori; Ohta Hidetoshi; Niitsu Yoshiro

CORPORATE SOURCE: Fourth Department Internal Medicine, Sapporo Medical University, Sapporo, Japan.. hira950712@aol.com

SOURCE: AMERICAN JOURNAL OF HEMATOLOGY, (2002 Feb) 69 (2) 138-40. Journal code: 7610369. ISSN: 0361-8609.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200202

ENTRY DATE: Entered STN: 20020212
Last Updated on STN: 20020222
Entered Medline: 20020221

AB The degree of acute **graft-versus-host** disease (**GVHD**) after allogeneic peripheral blood stem cell **transplantation** (allo-PBSCT) has been observed to be, unexpectedly, of an equal level to that after bone marrow **transplantation**. To explain this phenomenon, we hypothesized that granulocyte-colony stimulating factor (G-CSF) administration may induce transforming growth factor (**TGF**)-**beta** producing T cells in the donors. Five donors received 10 microg/kg G-CSF subcutaneously for 4 days. The **TGFbeta** mRNA expression in **CD4**(+) cells as measured by real time reverse transcription-polymerase chain reaction increased after G-CSF administration. This elevation is considered to be one additive mechanism of repression of acute **GVHD** after allo-PBSCT.

L5 ANSWER 5 OF 20 USPATFULL

ACCESSION NUMBER: 2001:229210 USPATFULL

TITLE: Methods for enhancing oral tolerance and treating autoimmune disease using inhibitors of interleukin-12

INVENTOR(S): Strober, Warren, Bethesda, MD, United States
Kelsall, Brian, Washington, DC, United States
Marth, Thomas, Kensington, MD, United States

PATENT ASSIGNEE(S): Government of the United States of America, Department of Health and Human Services (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001051159	A1	20011213
APPLICATION INFO.:	US 2000-732502	A1	20001207 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-284169, filed on 9 Apr 1999, ABANDONED A 371 of International Ser. No. WO 1996-US16007, filed on 11 Oct 1996, UNKNOWN

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: mary l. miller THE CANDLER BUILDING, needle & rosenberg, p.c., 127 peachtree street, n.e., atlanta, GA, 30303-1811

NUMBER OF CLAIMS: 20

EXEMPLARY CLAIM: 1

LINE COUNT: 1252

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for enhancing oral tolerance to an antigen associated with an autoimmune disease in a subject having the autoimmune disease comprising orally administering to the subject an antigen associated with the autoimmune disease and administering an

inhibitor of interleukin-12 in amounts sufficient to enhance oral tolerance. Also provided in the present invention is a method for treating or preventing an autoimmune disease in a subject comprising orally administering to the subject an antigen associated with the autoimmune disease and administering an inhibitor of interleukin-12 in amounts sufficient to treat or prevent the autoimmune disease, thereby treating or preventing the autoimmune disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 20 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001147668 MEDLINE
DOCUMENT NUMBER: 20584598 PubMed ID: 11154238
TITLE: Altered T-cell receptor + CD28-mediated signaling and blocked cell cycle progression in interleukin 10 and transforming growth factor-beta-treated alloreactive T cells that do not induce graft-versus-host disease.
AUTHOR: Boussiotis V A; Chen Z M; Zeller J C; Murphy W J; Berezovskaya A; Narula S; Roncarolo M G; Blazar B R
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Division of Medical Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.. vassiliki_boussiotis@macmailgw.dfci.harvard.edu
CONTRACT NUMBER: AI 41584 (NIAID)
AI 43552 (NIAID)
HL 54785 (NHLBI)
+
SOURCE: BLOOD, (2001 Jan 15) 97 (2) 565-71.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

AB The induction of anergy in T cells, although widely accepted as critical for the maintenance of tolerance, is still poorly understood at the molecular level. Recent evidence demonstrates that in addition to blockade of costimulation using monoclonal antibodies (mAbs) directed against cell surface determinants, treatment of mixed lymphocyte reaction (MLR) cultures with interleukin 10 (**IL-10**) and transforming growth factor-**beta** (**TGF-beta**) results in induction of tolerance, rendering alloreactive murine **CD4**(+) T cells incapable of inducing **graft-versus-host** disease (**GVHD**) after in vivo transfer to histoincompatible recipients. The present study, using these cells prior to adoptive transfer, determined that **IL-10** + **TGF-beta**-tolerant **CD4**(+) T cells exhibit an altered pattern of T-cell receptor (TCR) + CD28-mediated signaling and are incapable of progressing out of the G(1) phase of the cell cycle during stimulation with HLA class II disparate antigen-presenting cells. **TGFbeta** + **IL-10**-tolerant cells were incapable of phosphorylating TCR-zeta, or activating ZAP-70, Ras, and MAPK, similarly to T-cell tolerized by blockade of B7/CD28 and CD40/CD40L pathways. Moreover, these cells were incapable of clonal expansion due to defective synthesis of cyclin D3 and cyclin A, and defective activation of cyclin-dependent kinase (cdk)4, cdk6, and cdk2. These cells also exhibited defective down-regulation of p27(kip1) cdk inhibitor and lack of cyclin D2-cdk4 activation, Rb hyperphosphorylation, and progression to the S phase of the cell cycle. These data link anergy-specific proximal biochemical alterations and the downstream nuclear pathways that control T-cell expansion and provide a biochemical profile of **IL-10** +

TGF-beta-tolerant alloreactive T cells that do not induce **GVHD** when transferred into MHC class II disparate recipients in vivo.

L5 ANSWER 7 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

ACCESSION NUMBER: 2001:312012 BIOSIS
DOCUMENT NUMBER: PREV200100312012
TITLE: Use of IL-10 anergized T cells in haploidentical bone marrow transplantation.
AUTHOR(S): Bacchetta, Rosa (1); Zappone, Elisabetta (1); Zino, Elisabetta (1); Fleischhauer, Katharina (1); Blazar, Bruce R.; Narula, Satwant; Bordignon, Claudio (1); Roncarolo, Maria-Grazia (1)
CORPORATE SOURCE: (1) San Raffaele Telethon Institute for Gene Therapy, Milan Italy
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 581a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Transplantation** of haploidentical CD34+ purified stem cells in patients receiving highly immunosuppressive regimens results in hematopoietic engraftment without **GVHD**. However, these T- cell depleted **transplants** are associated with a poor immunological reconstitution with high risk for lethal infections, especially in adults. One strategy to overcome this complication is to induce anergy in donor derived T cells specific for host alloAgs, while preserving the rest of the T-cell repertoire. Induction of anergy through co-stimulatory blockade is presently under investigation in several preclinical and clinical studies. We previously showed that the immunosuppressive **cytokine IL-10**, induces alloAg specific anergy in human **CD4**+ T cells in vitro and promotes the generation of T regulatory type 1 (Tr1) cells that inhibit Ag-specific primary responses via **IL-10** and **TGF-beta** production.
Anergy was observed also in total human **PBMC** activated in vitro with fully HLA-mismatched APC in the presence of **IL-10**, but not of other immunosuppressive **cytokines** such as **TGF-beta**. In **IL-10** anergized cultures, the inhibition of Ag-specific proliferation ranged from 63 to 95% compared to that of control cells (pltoreq0,005), with a mean value of 81+-7; and it was associated with decreased CTLp frequencies to the specific alloAgs which ranged from 44 to 100% reduction, with a mean value of 71+-22. Comparable levels of T-cell anergy were obtained after stimulation with haploidentical APC in the presence of **IL-10**. AlloAg anergized T cells consistently preserved responses to other Ags, such as Tetanus Toxoid and Candida Albicans, demonstrating that the repertoire is not affected. In addition, preliminary results suggest that the frequencies of CTLps specific for viral peptides is increased after anergy induction. These in vitro results, together with the in vivo observation that adoptive transfer of **IL-10** + **TGF-beta** anergized T cells in mice resulted in a significant **GVHD** reduction, indicate that **IL-10** anergized T cells can be used to selectively modulate responses to the AlloAgs of the recipient. To ameliorate post **transplant** immunodeficiency without significant risk of **GVHD**, we started a pilot clinical study in patients who received haploidentical purified CD34+ stem cells infusing donor-derived T cells anergized to the alloAPC of the recipient by **IL-10** in vitro.

L5 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:299469 BIOSIS
DOCUMENT NUMBER: PREV200100299469
TITLE: Graft-versus-leukemia effect without graft-versus-host disease following delayed leucocyte injection in murine bone marrow chimeras: Role of cytokines and regulatory cells.
AUTHOR(S): Billiau, An D.; Sefrioui, Hassan; Rutgeerts, Omer; Peter, Vandenberghe; Waer, Mark
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 175a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Delayed infusion of donor lymphocytes (DLI) after bone marrow **transplantation** (BMT) has been shown clinically and experimentally to result in a **graft**-versus-leukemia (GVL) effect with reduced incidence of severe **graft-versus-host** disease (**GVHD**). Recently we corroborated this and showed that C3H fwdarwAKR minor histocompatibility antigen-mismatched BM chimeras failed to develop **GVHD** following DLI with 50 X 106 non-tolerant C3H splenocytes, 3 weeks after BMT. Nevertheless, DLI chimeras resisted a challenge with AKR leukemia cells, when infused within 3 weeks after DLI. In contrast, control chimeras rapidly succumbed due to leukemic disease. Moreover, we showed that host-reactive donor **CD4**+ cells persisted during three weeks elapsing after DLI, without, however, giving rise to host-reactive cytotoxic T lymphocytes. Here we studied the distinctive **cytokine** profile generated in the anti-host response of chimeric splenocytes after DLI and the possible role herein of regulatory cells, present in bone marrow chimeras. When challenged in vitro (MLR) with host-type cells, chimeric splenocytes failed to proliferate and produced only low levels of **cytokines** (as assessed by ELISA on MLR supernatant and RT-PCR on MLR cells). On the contrary, splenocytes of DLI chimeras, taken within one week after DLI, mounted low but significant anti-host MLR responses and produced high levels of Th1 (**IL-2**, IFN-gamma), Th2 (IL-4, IL-6, IL-13) **cytokines** and in particular of macrophage/monocyte **cytokines** (IL-1, TNF-alpha, iNOS) during MLR. Interestingly, these splenocytes produced, in contrast to the MLR **cytokine** profile of non-tolerant control C3H splenocytes, increasing levels (day 3 to 5 of MLR) of Th2 **cytokines** (IL-4, IL-5, IL-13), of iNOS and a continuously high level of macrophage/monocyte **cytokines** (IL-1, TNF-alpha, **TGF-beta**). A significant expansion of two large granular (LG) cell populations was clearly demonstrated by FACS analysis of peripheral blood and splenocytes of chimeric mice; these cells persisted in animals given DLI. In the spleen these LG cells comprised 55 +- 9 % and 63 +- 13 % in DLI resp. control chimeras versus 10 +- 2 % in untreated host-type mice. The majority of these LG cells expressed the Mac-1 antigen. Moreover, morphological analysis of these cells on cytospin preparations showed that they included numerous immature myeloid cells. We are currently exploring whether these LG cells play a role in the specific **cytokine** profile produced by DLI splenocytes upon recognition of host-type antigens and also whether these cells play a role in triggering GVL activity without **GVHD**.

L5 ANSWER 9 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999310327 MEDLINE
DOCUMENT NUMBER: 99310327 PubMed ID: 10382954
TITLE: Pre-treatment of transplant bone marrow cells with hydrocortisone and cyclosporin A alleviates

graft-versus-host reaction in a murine allogeneic host-donor combination.
AUTHOR: Grcevic D; Batinic D; Ascensao J L; Marusic M
CORPORATE SOURCE: Department of Physiology, Zagreb University School of Medicine, Croatia.
SOURCE: BONE MARROW TRANSPLANTATION, (1999 Jun) 23 (11) 1145-52. Journal code: 8702459. ISSN: 0268-3369.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

AB The aim of the study was to alleviate **graft-versus-host** reaction (GVHR) by pre-treatment of the bone marrow (BM) **transplant** with hydrocortisone (HC) and cyclosporin A (CsA) in C57BL/6J (donor) --> CBA/J (recipient) mouse combination. BM cells were exposed to HC and CsA for 1 h at 37 degrees C and then injected into lethally irradiated (9.5 Gy) mice at a dose of 2 x 10(6) BM cells/mouse. Haematopoietic recovery was assessed on day 12, and survival was followed for 100 days. Combinations of 1000 microg/ml HC and 100 microg/ml CsA, and 100 microg/ml HC and 10 microg/ml CsA significantly reduced MLR and additively mitigated GVHR in vivo, achieving 40% and 26% survival rates, respectively. However, HC and CsA altered neither the peripheral blood cell counts nor in vitro and in vivo BM cell clonogenic potential. Additional studies have shown that HC and CsA blocked con A-driven differentiation of **CD8**+ and **CD4**+ **CD8**+ lymph node cells (LNC) and progression of LNC to S + G2/M cell cycle phases, and inhibited IL-1, **IL-2** and **TGF-beta** while enhancing GM-CSF gene expression in BM cells. Taken together, these data indicate that the pre-treatment of the BM **transplant** with HC and CsA results in inactivation of GVHR effector cells and mitigation of GVHR while sparing BM repopulating capacity.

L5 ANSWER 10 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
ACCESSION NUMBER: 1999:176234 BIOSIS
DOCUMENT NUMBER: PREV199900176234
TITLE: Ex vivo IL10 and **TGF-beta** act synergistically to induce **CD4**+ aloantigen-specific tolerance resulting in diminished **graft-versus-host** diseease in vivo.
AUTHOR(S): Zeller, J. C. (1); Taylor, P. A.; Panoskaltsis-Mortari, A.; Murphy, W. J.; Ruscetti, R. W.; Narula, S.; Roncarolo, M. G.; Blazar, B. R.
CORPORATE SOURCE: (1) Dep. Pediatr., Univ. Minnesota, Minneapolis, MN 55455 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A614.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 11 OF 20 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-17303 DRUGU P
TITLE: Molecular basis of GVHD control induced by IL-10 and TGF-beta.
AUTHOR: Boussiotis V A; Murphy W; Zeller J; Berezovskaya A; Roncarolo

M; Chen Z M; Nadler L M; Blazar B R
CORPORATE SOURCE: Dana-Farber-Cancer-Inst.; Univ.Minnesota; TIGET
LOCATION: Boston, Mass.; Minneapolis, Minn., USA; Milan, It.
SOURCE: Blood (94, No. 10, Pt. 1 Suppl. 1, 604a, 1999)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Dana-Farber Cancer Institute, Boston, MA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2000-17303 DRUGU P
AB Using a murine model relevant to in-vivo pathophysiology, the Authors assessed the potential role of interleukin 10 (**IL-10**) and transforming growth factor **beta** (**TGF**-b) (alone and in combination) in therapeutic approaches for the induction of tolerance for bone marrow **transplantation** (BMT) and the molecular effects of these **cytokines** on T cells rendered anergic by such treatment. Ex-vivo treatment with **IL-10**/**TGF**-b induced specific biochemical alterations and it is suggested that these events might be responsible for the inability of such treated alloreactive **CD4**+ T cells to induce **GVHD** in-vivo. (conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).
ABEX CD4+ cells from B6 mice (as responders) and irradiated T cell depleted splenic cells from bm12 mice (as stimulators) were cultured in the presence of IL-10, TGF-b, IL-10/TGF-b or media. Although each cytokine had limited effect, their combination markedly reduced alloantigen specific response in primary and secondary MLR. Moreover, when adoptively transferred IL-10/TGF-b treated CD4+ B6 cells were markedly impaired in inducing GVHD lethality to MHC class II disparate recipients as compared to control primed-B6. To determine the molecular mechanism of hyporesponsiveness and the regulation of the cell cycle in the target cells, IL-10/TGF b-treated CD4+ B6-T cells were isolated prior to adoptive transfer and stimulated in-vitro. Stimulation of control B6 induced phosphorylation of TCR-zeta and activation of ZAP-70. In contrast, IL-10/TGF-b-treated B6 exhibited limited phosphorylation of TCR-zeta and defective activation of ZAP-70. In addition, the Ras pathway was activated in control but not in IL-10/TGF-b-treated cells as determined by defective activation of ERK1/ERK2 MAP kinases which are downstream of Ras. Moreover, IL-10/TGF-b-treated cells had increased p27kip1 cyclin-dependent kinase inhibitor and defective up-regulation of cyclin D3 and activation of its associated kinases cdk4 and cdk6 as compared to control B6 cells. (E54/RSV)

L5 ANSWER 12 OF 20 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999171692 MEDLINE
DOCUMENT NUMBER: 99171692 PubMed ID: 10073684
TITLE: Cell surface markers and circulating cytokines in graft versus host disease.
AUTHOR: Chang D M; Wang C J; Kuo S Y; Lai J H
CORPORATE SOURCE: Division of Rheumatology/Immunology/Allergy, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC.
SOURCE: IMMUNOLOGICAL INVESTIGATIONS, (1999 Jan) 28 (1) 77-86. Journal code: 8504629. ISSN: 0882-0139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 20000303
Entered Medline: 19990820
AB **Graft versus host** disease (**GVHD**)

remains the major obstacle to the widespread application of allogeneic bone marrow **transplantation** (BMT) despite improvement in drug prophylaxis. T cells in the donor bone marrow recognize and react against host alloantigens and thereby initiate **GVHD**, but the precise mechanisms by which host tissues are damaged remain unclear. In the current study, we determined the **cytokine** secretion, cell population distribution, and cell surface markers expression by ELISA and flow cytometer, to understand further the pathophysiology of **GVHD** . Our results demonstrated that there was no significant change in the cell ratio of B-and T- lymphocytes, and helper/suppressor cells during **GVHD** development when compared to the condition before **transplantation**. Furthermore, the percentage of natural killer cells, the interleukin-2 receptor (IL-2R) or the HLA-DR antigen on both **CD4** and **CD8** positive cells presented no significant difference between pre-**transplantation** and during **GVHD** . The serum **cytokine** secretion of IL-1, TNF-alpha, **IL-2**, ICAM-1, endothelin, **TGF-beta** showed no difference before BMT and during **GVHD**. However, when patients in the developing of **GVHD**, there was significant difference in the serum levels of soluble IL-2R (slL-2R), epidermal growth factor (EGF), and platelet derived growth factor (PDGF). In addition, with patients who develop **GVHD**, the mixed lymphocyte reaction also presented a significant difference. This study indicated that some serum **cytokines** such as sIL-2R, growth factors, and the mixed lymphocyte reaction may be used as parameters for the early detection of the development of **GVHD**.

L5 ANSWER 13 OF 20 USPATFULL

ACCESSION NUMBER:	1998:162315 USPATFULL
TITLE:	Recombinant pseudomonas exotoxin with increased activity
INVENTOR(S):	Pastan, Ira H., Potomac, MD, United States Fitzgerald, David J., Silver Springs, MD, United States
PATENT ASSIGNEE(S):	National Institutes of Health, Bethesda, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5854044		19981229
APPLICATION INFO.:	US 1995-463480		19950605 (8)

RELATED APPLN. INFO.:	Division of Ser. No. US 1995-405615, filed on 15 Mar 1995, now patented, Pat. No. US 5602095 which is a continuation of Ser. No. US 1992-901709, filed on 18 Jun 1992, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Prouty, Rebecca E.
LEGAL REPRESENTATIVE:	Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS:	13
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	14 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT:	1346

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the production and use of recombinant Pseudomonas-derived toxins modified to increase their toxicity and potency in therapy. More particularly, the invention relates to certain deletions in domain II of the amino acid sequence of Pseudomonas exotoxin the domain which relates to the toxin's natural proteolytic processing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 14 OF 20 USPATFULL

ACCESSION NUMBER:	1998:124562 USPATFULL

TITLE: Recombinant pseudomonas exotoxin with increased activity

INVENTOR(S): Pastan, Ira H., Potomac, MD, United States
Fitzgerald, David J., Silver Springs, MD, United States

PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5821238		19981013
APPLICATION INFO.:	US 1995-461234		19950605 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-405615, filed on 15 Mar 1995 which is a continuation of Ser. No. US 1992-901709, filed on 18 Jun 1992, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Feisee, Lila
ASSISTANT EXAMINER: Lucas, John
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1,6
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1337
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the production and use of recombinant Pseudomonas-derived toxins modified to increase their toxicity and potency in therapy. More particularly, the invention relates to certain deletions in domain II of the amino acid sequence of Pseudomonas exotoxin the domain which relates to the toxin's natural proteolytic processing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 15 OF 20 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998238502 MEDLINE
DOCUMENT NUMBER: 98238502 PubMed ID: 9577641
TITLE: An analysis of sclerodermatous **graft-versus-host**-disease after allogeneic bone marrow **transplantation**: **CD8**+CD57+T-cell proliferation and increased production of **TGF-beta**.
AUTHOR: Nakazawa Y; Koike K; Kitazawa Y; Sakashita K; Sawai N; Matsumoto K; Ito S; Kumagai T; Yamada M; Komiyama A
CORPORATE SOURCE: Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan.
SOURCE: RINSHO KETSUEKI. JAPANESE JOURNAL OF CLINICAL HEMATOLOGY, (1998 Mar) 39 (3) 185-92.
Journal code: 2984782R. ISSN: 0485-1439.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 19980708
Entered Medline: 19980622

AB A 19-year-old woman with acute lymphoblastic leukemia received an allogeneic bone marrow **transplantation** (BMT) from an HLA-identical sibling during the second remission, on September 28, 1993. The conditioning regimen consisted of total body irradiation and cyclophosphamide. Short term methotrexate and cyclosporin A were given for prophylaxis of **graft-versus-host** disease (**GVHD**). On day 771 after BMT, she complained of bilateral forearm

pain, and developed sclerotic lesions on the skin of the abdominal wall, forearms and legs. The diagnosis of sclerodermatous **GVHD** was established by skin biopsy on day 834. The values of CRP and IgG were elevated, and both antinuclear antibody and anti-DNA antibody became positive. Flow cytometric analysis showed a significant increase in the number of CD57+ cells after appearance of sclerotic change. In addition, 65% of **CD8**+ cells were positive for CD57. Circulating level of transforming growth factor (**TGF**)-**beta** 1 was high. These results suggest that overproduction of **CD8**+ CD57+ T cells and high level of circulating **TGF**-**beta** are related to the development of sclerodermatous **GVHD**.

L5 ANSWER 16 OF 20 USPATFULL
ACCESSION NUMBER: 97:47503 USPATFULL
TITLE: Fusion proteins comprising circularly permuted ligands
INVENTOR(S): Pastan, Ira H., Potomac, MD, United States
Kreitman, Robert J., Potomac, MD, United States
Puri, Raj K., North Potomac, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5635599		19970603	
APPLICATION INFO.:	US 1994-225224		19940408	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Walsh, Stephen G.
ASSISTANT EXAMINER: Kemmerer, Elizabeth C.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 1966
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides for circularly permuted ligands which possess specificity and binding affinity comparable to or greater than the specificity and binding affinity of the original (unpermuted) ligand. The invention further provides for novel fusion proteins comprising a circularly permuted ligand fused to one or more proteins of interest.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 17 OF 20 USPATFULL
ACCESSION NUMBER: 97:12434 USPATFULL
TITLE: Recombinant pseudomonas exotoxin with increased activity
INVENTOR(S): Pastan, Ira H., Potomac, MD, United States
Fitzgerald, David J., Silver Springs, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5602095		19970211	
APPLICATION INFO.:	US 1995-405615		19950315	(8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-901709, filed on 18 Jun 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted

PRIMARY EXAMINER: Low, Christopher S. F.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1344
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the production and use of recombinant Pseudomonas-derived toxins modified to increase their toxicity and potency in therapy. More particularly, the invention relates to certain deletions in domain II of the amino acid sequence of Pseudomonas exotoxin the domain which relates to the toxin's natural proteolytic processing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 18 OF 20 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97436575 MEDLINE
DOCUMENT NUMBER: 97436575 PubMed ID: 9292548
TITLE: In vitro generation of allospecific human CD8+ T cells of Tc1 and Tc2 phenotype.
AUTHOR: Halverson D C; Schwartz G N; Carter C; Gress R E; Fowler D H
CORPORATE SOURCE: Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: BLOOD, (1997 Sep 1) 90 (5) 2089-96.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19970930
AB We have previously shown that allospecific murine **CD8**+ T cells of the Tc1 and Tc2 phenotype could be generated in vitro, and that such functionally defined T-cell subsets mediated a **graft**-versus-leukemia (GVL) effect with reduced **graft-versus-host** disease (**GVHD**). To evaluate whether analogous Tc1 and Tc2 subsets might be generated in humans, **CD8**+ T cells were allostimulated in the presence of either interleukin-12 (IL-12) and transforming growth factor-**beta** (**TGF-beta**) (Tc1 culture) or IL-4 (Tc2 culture). Tc1-type **CD8** cells secreted the type I **cytokines IL-2** and interferon gamma (IFN-gamma), whereas Tc2-type cells primarily secreted the type II **cytokines** IL-4, IL-5, and **IL-10**. Both **cytokine**-secreting populations effectively lysed tumor targets when stimulated with anti-T-cell receptor (TCR) antibody; allospecificity of Tc1- and Tc2-mediated cytolytic function was demonstrated using bone marrow-derived stimulator cells as targets. In addition, both Tc1 and Tc2 subsets were capable of mediating cytolysis through the fas pathway. We therefore conclude that allospecific human **CD8**+ T cells of Tc1 and Tc2 phenotype can be generated in vitro, and that these T-cell populations may be important for the mediation and regulation of allogeneic **transplantation** responses.

L5 ANSWER 19 OF 20 FEDRIP COPYRIGHT 2002 NTIS
ACCESSION NUMBER: 2002:137819 FEDRIP
NUMBER OF REPORT: CRISP 1Z01BC09264-18
RESEARCH TITLE: **Cytokine** Regulation of Normal and Neoplastic Hematopoietic Cell Growth
STAFF: Principal Investigator: RUSCETTI, FRANCIS W.; NCI BC, NIH

SUPPORTING ORGN: Supported By: DIVISION OF BASIC SCIENCES - NCI
FISCAL YEAR: 2001
FUNDING: Not Applicable
FILE SEGMENT: National Institutes of Health
SUM We and others have shown that to initiate and maintain the growth and differenti ation of primitive progenitor cells, multiple **cytokine** stimulation (synergy) is required. More recently, we showed that such cooperation also occurs between neg ative regulators of cell growth, and that the ability of primitive progenitors t o proliferate depends on the balance of positive and negative signals the cell r eceives. Transforming growth factor **beta** (**TGF**?) directly and reversibly inhibits hematopoietic stem cells with marrow repopulating ability (LT-HSC). Also, short -term incubation with antibody and antisense to **TGF**? stimulates the self-renewal potential of these stem cells. **TGF**? has inhibitory effects on the cell surface expression of many **cytokine** receptors that directly correlates with its effect o n cell growth. For example, stem cell factor receptor (c-kit) expression is down regulated by **TGF**?, in part by affecting c-kit mRNA stability. These results indi cated that c-kit expression couldbe negatively regulated on LT-HSC. Indeed, we w ere able to characterize a novel LT-HSC lacking c-kit expression and that in bon e marrow cell development, this cell matures into a c-kit+ LT-HSC. Also, **TGF**? pr events S phase cell-cycle progression through an intracellular mechanism involvi ng regulation of transcription factors and cell-cycle regulatory proteins. In vi vo results demonstrated that **TGF**? can protect mice from both the lethal hematopo ietic toxicity of 5-FU, as well as the nonhematopoiesis toxicity of DXR. These f indings show that a negative regulator of hematopoiesis can be successfully used systemically to mediate chemoprotecti on in vivo. Previous results from many lab s also indicated that **TGF**? treatment of donor cells before bone marrow transplan tation (BMT) could have a beneficial effect by blocking the immune reactivity. W e were able to show suppression of **graft** vs host disease (**GVHD**) after allogeneic B MT through a **TGF** ? mediated mechanism. Treatment of donor **CD4** T-cells with **TGF**? and **IL-10** made the donor T-cells hyporesponsive and less able to promote **GVHD**. In many instances, growth inhibition following terminal differentiation or anti-cancer drug treatment results in apoptosis (programmed cell death).

L5 ANSWER 20 OF 20 FEDRIP COPYRIGHT 2002 NTIS
ACCESSION NUMBER: 2002:36530 FEDRIP
NUMBER OF REPORT: VA 123765
NUMBER OF CONTRACT: 0001, 512
RESEARCH TITLE: Role of T Cells in a Model of Scleroderma Lung Disease
STAFF: Principal Investigator: Yurovsky, Vladimir V., Ph.D.
PERFORMING ORGN: Department of Veterans Affairs, Medical Center, Baltimore, MD
SUPPORTING ORGN: Supported By: Department of Veterans Affairs, Research and Development (15), 810 Vermont Ave. N.W., Washington, D.C., 20420, United States of America
PROJECT START DATE: Oct 23, 1997
FILE SEGMENT: Department of Veterans Affairs
SUM T-LYMPHOCYTES; SCLERODERMA, SYSTEMIC; LUNG DISEASES Final Report Title: Role of T Cells in a Model of Scleroderma Lung Disease OBJECTIVES: The goal of this study is to analyze the T cell repertoir e and **cytokine** production in the peripheral blood and bronchoalveolar lavage (BAL) fluid from patients receiving hematopoietic stem cell **transplants** and to compare with systemic sclerosis (scleroderma) patients. RESEARCH DESIGN: Eleven patients have been enrolled into the study wh o develop noninfectious pulmonary inflammation following blood and marrow **transplantation**. BAL has been done on all patients. Peripheral blood was obtained from two patients. Leftover BAL samples and blood samples were used for flow cytometry analysis, isolation of

CD4' and **CD8**' T cells, and analysis of relative expression of T cell antigen receptor (TCR) variable (V) gene families and diversity of TCR junctional region lengths. METHODOLOGY: The numbers and percent of CD3' T cells bearing **CD4**, C D8, 78TCR, and activation markers CD25 and HLA-DR were determined by two-color flow cytometry. Positive selection of **CD8**' and **CD4**' T cells was performed with sequential use of **CD8** and **CD4** Dynabeads (Dynal Inc.). Total cellular RNA was isolated from unfractionated, **CD4**', and **CD8**' T cells, reverse transcribed using random primer hexamers, and amplified by polymerase chain reaction (PCR), using TCR-specific or **cytokine**-specific primer pairs. 32p-labeled PCR products were analyzed by electrophoresis in agarose or polyacrylamide gels. The expression of interleukin (**IL**)-**2**, IL-4, IL-5, **IL**- **10**, interferon y (IFNy), and transforming growth factor P (**TGFP**) mRNA was analyzed in two patients, using PCR with P-actin as an internal standard. FINDINGS: Nearly all TCR V(x and VP gene families were detected in th e blood and BAL fluids from bone marrow **transplant** recipients. Some TCR V gene families were expressed in oligoclonal manner in both **CD4**' and **CD8**' BAL T cells, as assessed by limited diversity of TCR junctional region lengths. DNA sequencing confirmed the oligoclonal character of expansion of BAL T cells bearing a particular TCR; that suggests an antigen-driven selection of these T cells. Transcripts for all **cytokines**, except IL-5, were found in the peripheral blood from two patients. **IL-2**, **IL-10**, IFNy, and **TGFP** mRNA were expressed in unfractionated and **CD8**' T cells from BAL fluids, while only IL-4 and **TGFP** mRNA were detected in **CD4**' BAL T cells. **CD8**' T cells expressing TCRBV5S2 gene segment that have been clonally expanded in the lungs of two **transplant** recipients were isolated and cloned. **CD8**' T cell clones were also generated from BAL fluids from systemic sclerosis patients and tested for functional activities, including autoreactivity, cytotoxicity, and production of **cytokines**. Co-culture experiments with lung fibroblasts showed that some **CD8**' T cell clones stimulated collagen mRNA production in fibroblasts and expressed low levels of cytotoxic activity against fibroblasts. These data suggest that a particular subset of **CD8**' T cells in the lungs may stimulate collagen production in fibroblasts that are resistant to killing by the same T cells. Possible mechanisms of enhancing collagen production include secretion of type 2 **cytokines** or other soluble mediators, and cell-cell contacts. CLINICAL RELATIONSHIPS: Immunologic similarities between the lung dis ease in systemic sclerosis and the lung involvement in chronic **graft-versus-host** disease following hematopoietic stem cell **transplantation** make the latter a helpful model to study the pathophysiologic processes in the lungs and may provide an idea of the nature of antigens initiating and perpetuating the lung disease. The results of this study should potentially form the basis for the development of new therapeutic approaches for the treatment of fibrotic lung diseases.

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